1 FW

Docket No. BULK 3.0-049

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Buchi Reddy REGURI et al.

Application No.: 10/748,865

Filed: December 30, 2003

For: IMPROVED PROCESS FOR PREPARATION OF MONTELUKAST AND ITS SALTS

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

TRANSMITTAL LETTER

To complete the requirements of the priority claim under 35 U.S.C. § 119 for the subject application, applicants are submitting herewith a certified copy of India Patent Application No. 993/MAS/2002, filed December 30, 2002.

If there are any questions regarding this submission, please contact the undersigned.

Respectfully submitted

Robert A. Franks
Reg. No. 28,605
Attorney for Applicants

May 25, 2005

Dr. Reddy's Laboratories, Inc.
200 Somerset Corporate Blvd., Seventh Floor
Bridgewater, New Jersey 08807-2862
Telephone 908-203-6504
Facsimile 908-203-6515

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Provisional Specification, Complete Specification & Abstract of the extract of Patent Application No.993/MAS/2002, dated 30/12/2002 by M/s. Dr. Reddy's Laboratories Limited, having its registered office at 7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh, India.

.....

.....In witness thereof

I have hereunto set my hand

Dated this the 19th day of July 2004

M.S. Venkataraman

(M.S. VENKATARAMAN)
Assistant Controller of Patents & Designs

PA[illegible]T [illegible]FICE BRANCH
GO[illegible]RN[illegible]NT OF INDIA
Gun[illegible]om[illegible]x, 6th Floor, Annex.II
No.4[illegible] An[illegible] Salai, Teynampet, Chennai – 600 018

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)
APPLICATION FOR GRANT OF A PATENT
(Section 5(2), 7, 54 and 135 and Rule 33A)

1. I/We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016
2. hereby declare -
   (a) that ~~I am~~/ we are in possession of an invention titled "**Novel Process for the Preparation of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl]ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl] cyclopropaneacetic acid (Montelukast) and its pharmaceutically acceptable salts**"
   (b) that the Provisional/~~Complete~~ specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to ~~me~~/us.
3. further declare that the inventor(s) for the said invention ~~is~~/are **Buchi Reddy Reguri, Satyanarayana Bollikonda, Veera Venkata Naga Chandra Sekhar Bulusu, Ravi Kumar Kasturi and Sanjeev Kumar Aavula.** All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh.**
4. I/We claim the priority from the application(s) filed in convention countries, particulars of which are as follows.
5. I/We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which I/We are the applicant/~~patentee~~
6. I/We state that the application is divided out of ~~my~~/our application, the particulars of which are given below and pray that this application deemed to have been filed on _____ under section 16 of the Act.
7. *That ~~I am~~/We are the assignee or ~~legal representative~~ of the true and first inventors.*
8. That ~~my~~/our address for service in India is as follows:

Dr. R. Buchi Reddy,
Director-R&D,
Dr. Reddy's Laboratories Limited
7-1-27, Ameerpet
Hyderabad, A.P., 500 016
Phone: 040- 3095578
Fax: 040-3095438

9. Following declaration was given by the inventor(s) or ~~applicant(s)~~ in the convention country:
I/We, the true and first inventors for this invention or ~~the applicant(s)~~ in the convention country declare that the applicant(s) herein ~~is~~/are ~~my~~/our assignee or legal representative .

(Signed)_____
Buchi Reddy Reguri,
404, Balaji Residency,
88/A MIGH,
Vengal Rao Nagar,
Hyderabad-500 038.

(Signed)_____
Satyanarayana Bollikonda,
H.No. 5-172,
Deepthisri nagar,
Chandanagar,
Hyderabad-500 050.

(Signed)_____
Veera Venkata Naga Chandra Sekhar Bulusu,
Plot No. 19,
GMSD colony,
Vivekananda Nagar,
Kukatpally,
Hyderabad-500 072.

(Signed)_____
Ravi Kumar Kasturi,
H. No. 2-22-190/A,
Jaya nagar colony,
Kukatpally,
Hyderabad – 500 072.

(Signed)_____
Sanjeev Kumar Aavula,
H.No. 312 EWS,
Bharatnagar colony,
Hyderabad-500 018.

10. That to the best of ~~my~~/our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to ~~me~~/us on this application.

11. Following are the attachments with the application
    (a) Provisional/~~Complete~~ specification (--09- pages, in triplicate)
    (b) Drawings (------ pages, in triplicate)
    (c) Priority documents(s) —
    (d) Statement and Undertaking on Form-3. —
    (e) Power of authority —
    (f) Abstract of the invention (------- page, in triplicate)
    (g) Fee Rs. 5000.00 (five thousand rupees only) in Cash/cheque/bank draft bearing No.336806 dated 24.12.2002 drawn on HDFC Bank Limited, Lakdi-ka-pool, Hyderabad – 4.

I/We request that a patent may be granted to me/us for the said invention.

Dated this 24th day of December 2002.

(Signed) MBReddy

To,
The Controller of Patents
The Patents Office Branch, Chennai.

Dr. Reguri Buchi Reddy,
Director (R&D),
Dr. Reddy's Laboratories Limited.

FORM-2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(SECTION 10)

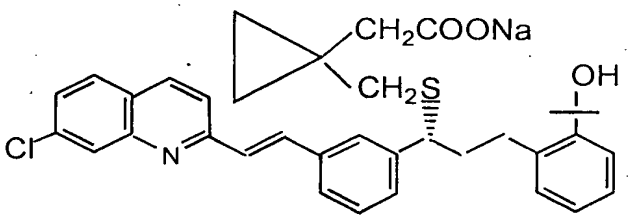
Novel Process for the Preparation of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl]ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl] cyclopropaneacetic acid (Montelukast) and its pharmaceutically acceptable salts

Dr. Reddy's Laboratories Limited,
An Indian Company having its registered office at
7-1-27, Ameerpet,
Hyderabad-500 016, A.P., India.

The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

FIELD OF THE INVENTION:

The present invention relates to Novel process for the preparation of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl]ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl] cyclopropaneacetic acid (commonly known as Montelukast) and its pharmaceutically acceptable salts, preferably sodium salt. It may be represented as Formula (I).



Formula (I)

BACK GROUND OF THE INVENTION:

Montelukast sodium is a Leukotriene antagonist and is useful in the treatment of Asthma and as well as other conditions mediated by leukotrienes, such as inflammation and allergies.

EP 480717 discloses certain substituted quinoline compounds including [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast sodium), methods for their preparation and methods of pharmaceutical formulations using these compounds in mammals especially humans.

The process for the preparation comprises of reacting 2-(2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl)-ethenyl) phenyl)-3-(methanesulfonyloxy) propyl) phenyl)-2-propoxy) tetra hydro pyran with Methyl 1-(acetylthiomethyl) cyclopropane acetate in presence of

hydrazine, cesium carbonate in acetonitrile as solvent to get methyl ester of Montelukast in pyran protected form. The protected compound is further reacted with pyridinium p-toluene sulfonate, sodium hydroxide in a mixture of methanol and tetrahydrofuran as a solvent to afford Montelukast sodium of Formula (I).

US 5,614,632 claimed an improved process for the preparation of Montelukast sodium salt including the process for the preparation of its key intermediates. The process comprises, the generation of dilithium dianion of 1-(mercaptomethyl) cyclopropaneacetic acid then condensation with 2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl) ethenyl) phenyl)-3-methanesulfonyloxypropyl) phenyl)-2-propanol (referred as mesylated alcohol) to afford the Montelukast. It is further converted to its corresponding sodium salt via dicyclohexyl amine salt. The patent also discloses the process for the preparation of mesylated alcohol, which comprises reacting Methyl 2-(3 (S)-(3-(2-(7-chloro-2-quinolinyl) ethenyl) phenyl)-3- hydroxy propyl) benzoate with methyl magnesium chloride to give diol, which is further converted to mesylated alcohol on reaction with methane sulfonyl chloride. The process for the preparation of above described benzoate is disclosed in EP 480717 (example 146, step-2), which involves the usage of (-) B-chloro diisopinocampheylborane as a chiral reducing agent.

The said patent also claims the process for the preparation of crystalline Montelukast sodium salt.

Many other related patents disclose the process for the preparation of Montelukast and its intermediates but none of those patents are related to the process of the present invention. The prior art procedures involves more number of steps which includes the protection and further deprotection of diol intermediate, the usage of hazardous and costly raw

materials such as n-butyl lithium in typical reaction conditions i.e., at very low temperatures (-25^{O}C). The processes of the prior art references involve tedious workup to isolate the required product and thus results in excess time cycle, which in turn rendering the process more costly and less eco friendly thus the process is not recommendable for commercial scale up.

As the Montelukast sodium of Formula (I), which is useful in the treatment of Asthma, hence, it is important to have a cost effective and commercially viable in a novel method for preparing the compound of Formula (I).

Therefore, the main objective of the present invention is to prepare Montelukast sodium in novel method, which is cost-effective, commercially viable and non-hazardous.

The Montelukast sodium prepared in the present novel process is having amorphous nature with enough chiral purity, which is suitable for pharmaceutical formulations.

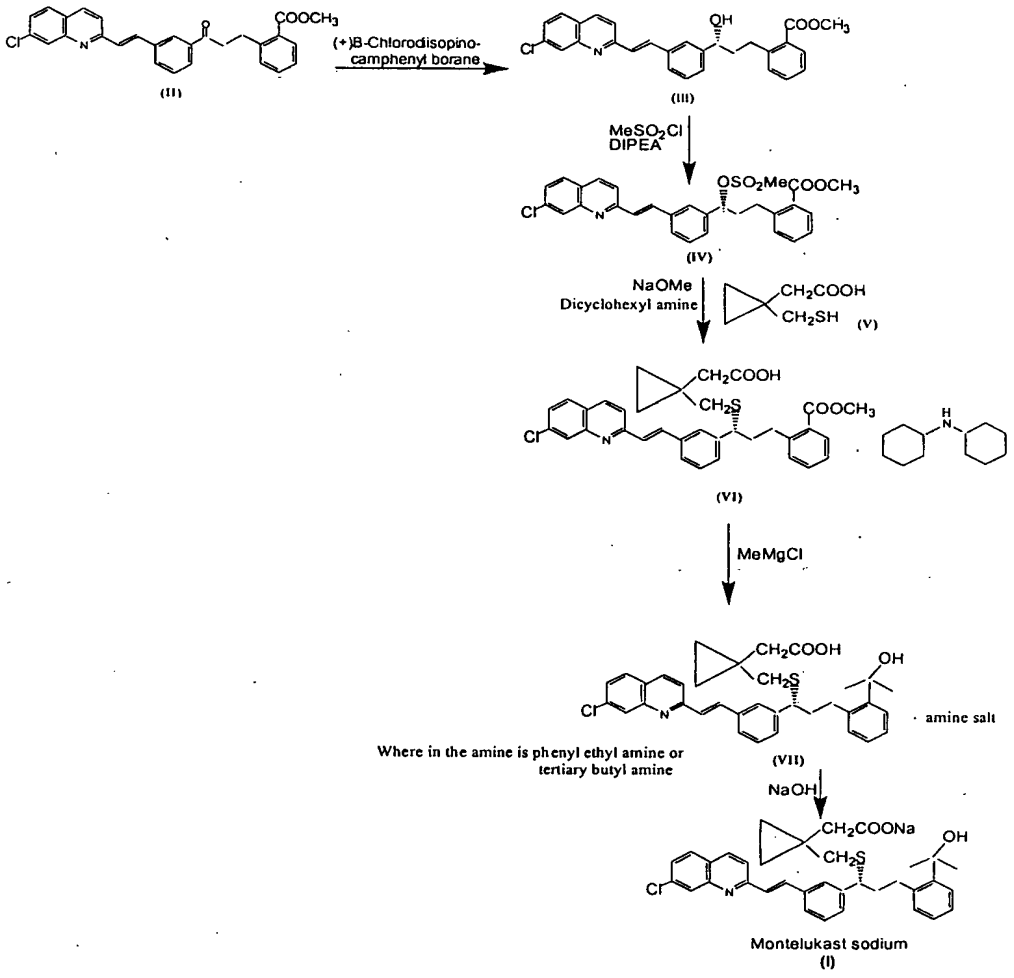
SUMMARY OF THE INVENTION:

The present invention provides an improved process for the preparation of Montelukast and its pharmaceutically acceptable salts, preferably sodium salt. The novel process of the present invention comprises, the reduction of Methyl-2-(3-(3'-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-oxopropyl benzoate using (+) B-chloro diisopinocampheylborane as a chiral reducing reagent and the resultant alcohol is mesylated followed by condensation with 1-mercapto methyl cyclopropane acetic acid to give an ester compound. The ester is reacted with methyl magnesium chloride to afford Montelukast and is isolated in the form of phenyl ethylamine or tertiary butyl amine salt. The amine salt of Montelukast is converted into sodium salt of Montelukast in a conventional method.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention relates to a novel and improved process for the preparation of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl]ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl] cyclopropaneacetic acid (commonly known as Montelukast) and its pharmaceutically acceptable salts, preferably sodium salt.

The process of the present invention is schematically represented as follows.



Methyl-2-(3-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-oxopropyl benzoate of Formula (II) is reduced with (+) B-chloro diisopinocampheylborane as a chiral reducing reagent in polar organic solvents to result Methyl-2-(3-(3-(2-(7-chloro-2-

formula (III) is mesylated with methane sulfonyl chloride in a mixture of polar and non-polar organic solvents to form Methyl-2-(3-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-methane sulfonyloxy propyl benzoate of formula (IV), which is then condensed with 1-mercapto methyl cyclopropane acetic acid of formula (V) in mixture of polar organic solvents in presence of base and is isolated in the form of organic amine salt of formula (VI). The resultant amine salt is reacted with methyl magnesium chloride in an organic solvent and is again isolated in the form of organic amine salt of formula (VII). The amine salt of Montelukast of formula (VII) is conveniently converted into pharmaceutically acceptable salts, preferably sodium salt using sodium methoxide or sodium hydroxide. Accordingly, the present invention provides an improved process for the preparation of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl]ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl] cyclopropaneacetic acid (commonly known as Montelukast) and its pharmaceutically acceptable salts, preferably sodium salt, which comprises;

a) adding (+) B-chloro diisopinocampheylborane (a chiral reducing agent) to a haloalkane solvent comprising of dichloromethane, dichloroethane or chloroform, preferably dichloromethane or an ethereal solvent such as tetrahydrofuran under nitrogen atmosphere at a temperature of –25 to +20°C, preferably –5 to 0°C;

b) adding the solution of Methyl-2-(3-(3-(2-(7-chloro-2-quinolinyl) ethenyl) phenyl)-3-oxopropyl benzoate of Formula (II) in organic solvent described as in step (a), followed by stirring the mass till the reaction substantially completes;

c) further quenching the mass with either organic or inorganic base and subsequent work up to get an alcohol of formula (III);

d) reacting the alcohol obtained in step (c) with methane sulfonyl chloride in presence of tertiary amines comprising of diisopropyl ethyl amine or triethyl amine as base in a mixture of polar and non-polar organic solvents at a temperature of 0-75^{O}C;

e) stirring the reaction mass obtained in step (d) till the reaction substantially completes and subsequent work up to get mesylated compound of formula (IV);

f) reacting mesylated compound of formula (IV) with 1-mercapto methyl cyclopropane acetic acid of formula (V) in polar organic solvents in presence of base such as sodium methoxide, sodium ethoxide, sodium hydride or n-butyl lithium at a temperature of 30-90^{O}C;

g) stirring the reaction mass obtained in step (f) till the reaction substantially completes and subsequent work up to get crude ester compound and further reaction with dicyclohexyl amine salt to afford the amine salt of formula (VI);

h) treating the amine salt of formula (VI) with an organic acid such as acetic acid and further reaction with methyl magnesium chloride or methyl magnesium bromide in an organic solvent at a temperature of –10 to +30^{O}C;

i) stirring the reaction mass obtained in step (h) till the reaction substantially completes and subsequent work up to get crude Montelukast and further reaction with primary, secondary or tertiary amines, preferably tertiary butyl amine or phenyl ethyl amine to afford the amine salt of formula (VII);

reaction with primary, secondary or tertiary amines, preferably tertiary butyl amine or phenyl ethyl amine to afford the amine salt of formula (VII);

j) optionally purifying the compound obtained in step (i) in the form of amine salt or free acid in an organic solvent or mixtures thereof;

k) converting the amine salt or free acid of Montelukast into its pharmaceutically acceptable salts in conventional methods.

The polar organic solvents mentioned in the step (d) of the above process comprises of halogenated solvents such as dichloromethane, dichloroethane, chloroform OR nitrile solvents such as acetonitrile, propionitrile OR dimethyl formamide, tetra hydrofuran and inorganic solvents comprising of hexane, toluene or ethyl benzene.

The polar organic solvents mentioned in the step (d) of the above process comprises of straight or branched chain alcohols having C1-C4 carbon atoms such as methanol, ethanol, n-propanol, iso propanol, n-butanol, tertiary butanol OR dimethyl formamide, dimethyl sulfoxide, dimethyl acetamide and tetra hydrofuran either in individual form or mixtures thereof.

The organic solvents mentioned in the step (j) of the above process comprises of straight or branched chain alcohols having C1-C4 carbon atoms such as methanol, ethanol, n-propanol, iso propanol, n-butanol, tertiary butanol OR nitrile solvents such as acetonitrile, propionitrile OR halogenated solvents such as dichloromethane, dichloroethane, chloroform OR toluene, ethyl acetate and tetrahydrofuran either in individual form or mixtures thereof.

The Montelukast sodium obtained in the present novel process is having >99.0% enantiomeric excess purity and resulted in amorphous form. The Montelukast sodium obtained in the present novel process is also free flowing and non-solvated solid; hence it is well suited for pharmaceutical applications.

The process of the present invention is cost effective, eco-friendly and well suited for scale up.

Dated this day of December 2002.

Signed) _____
(Dr. Reguri Buchi Reddy),
Director (R&D),
Dr. Reddy's Laboratories Limited.

FORM-2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(SECTION 10)

Novel Process for the Preparation of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid (Montelukast) and its pharmaceutically acceptable salts

Dr. Reddy's Laboratories Limited,
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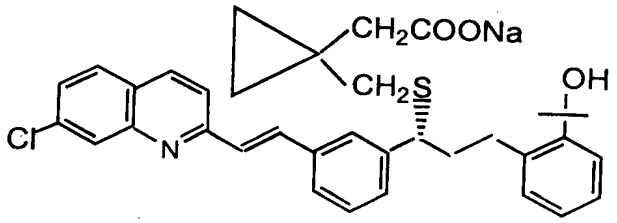
7-1-27, Ameerpet,
Hyderabad-500 016, A.P., India.

The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

FIELD OF THE INVENTION:

The present invention relates to novel process for the preparation of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl] propyl] thio] methyl] cyclopropaneacetic acid (commonly known as Montelukast) and its pharmaceutically acceptable salts, preferably sodium salt. It may be represented as Formula (I).



Formula (I)

BACK GROUND OF THE INVENTION:

Montelukast sodium is a Leukotriene antagonist and is useful in the treatment of Asthma and as well as other conditions mediated by leukotrienes, such as inflammation and allergies.

EP 480717 discloses certain substituted quinoline compounds including [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast sodium), methods for their preparation and methods of pharmaceutical formulations using these compounds in mammals especially humans.

The process for the preparation comprises of reacting 2-(2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl)-ethenyl) phenyl)-3-(methanesulfonyloxy) propyl) phenyl)-2-propoxy) tetra hydro pyran with Methyl 1-(acetylthiomethyl) cyclopropane acetate in presence of

hydrazine, cesium carbonate in acetonitrile as solvent to get methyl ester of Montelukast in pyran protected form. The protected compound is further reacted with pyridinium p-toluene sulfonate, sodium hydroxide in a mixture of methanol and tetrahydrofuran as a solvent to afford Montelukast sodium of Formula (I).

US 5,614,632 claimed an improved process for the preparation of Montelukast sodium salt including the process for the preparation of its key intermediates. The process comprises, the generation of dilithium dianion of 1-(mercaptomethyl) cyclopropaneacetic acid then condensation with 2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl) ethenyl) phenyl)-3-methanesulfonyloxypropyl) phenyl)-2-propanol (referred as mesylated alcohol) to afford the Montelukast. It is further converted to its corresponding sodium salt via dicyclohexyl amine salt. The patent also discloses the process for the preparation of mesylated alcohol, which comprises reacting Methyl 2-(3 (S)-(3-(2-(7-chloro-2-quinolinyl) ethenyl) phenyl)-3-hydroxy propyl) benzoate with methyl magnesium chloride to give diol, which is further converted to mesylated alcohol on reaction with methane sulfonyl chloride. The process for the preparation of above described benzoate is disclosed in EP 480717 (example 146, step-2), which involves the usage of (-) B-chloro diisopinocampheylborane as a chiral reducing agent.

The said patent also claims the process for the preparation of crystalline Montelukast sodium salt.

Many other related patents disclose the process for the preparation of Montelukast and its intermediates but none of those patents are related to the process of the present invention. The prior art procedures involves more number of steps which includes the protection and further deprotection of diol intermediate, the usage of hazardous and costly raw materials

such as n-butyl lithium in typical reaction conditions i.e., at very low temperatures (-25°C). The processes of the prior art references involve tedious workup to isolate the required product and thus results in excess time cycle, which in turn rendering the process more costly and less eco friendly thus the process is not recommendable for commercial scale up. As the Montelukast sodium of Formula (I), which is useful in the treatment of Asthma, hence, it is important to have a cost effective and commercially viable in a novel method for preparing the compound of Formula (I).

Therefore, the main objective of the present invention is to prepare Montelukast sodium in novel method, which is cost-effective, commercially viable and non-hazardous.

The Montelukast sodium prepared in the present novel process is having amorphous nature with enough chiral purity, which is suitable for pharmaceutical formulations.

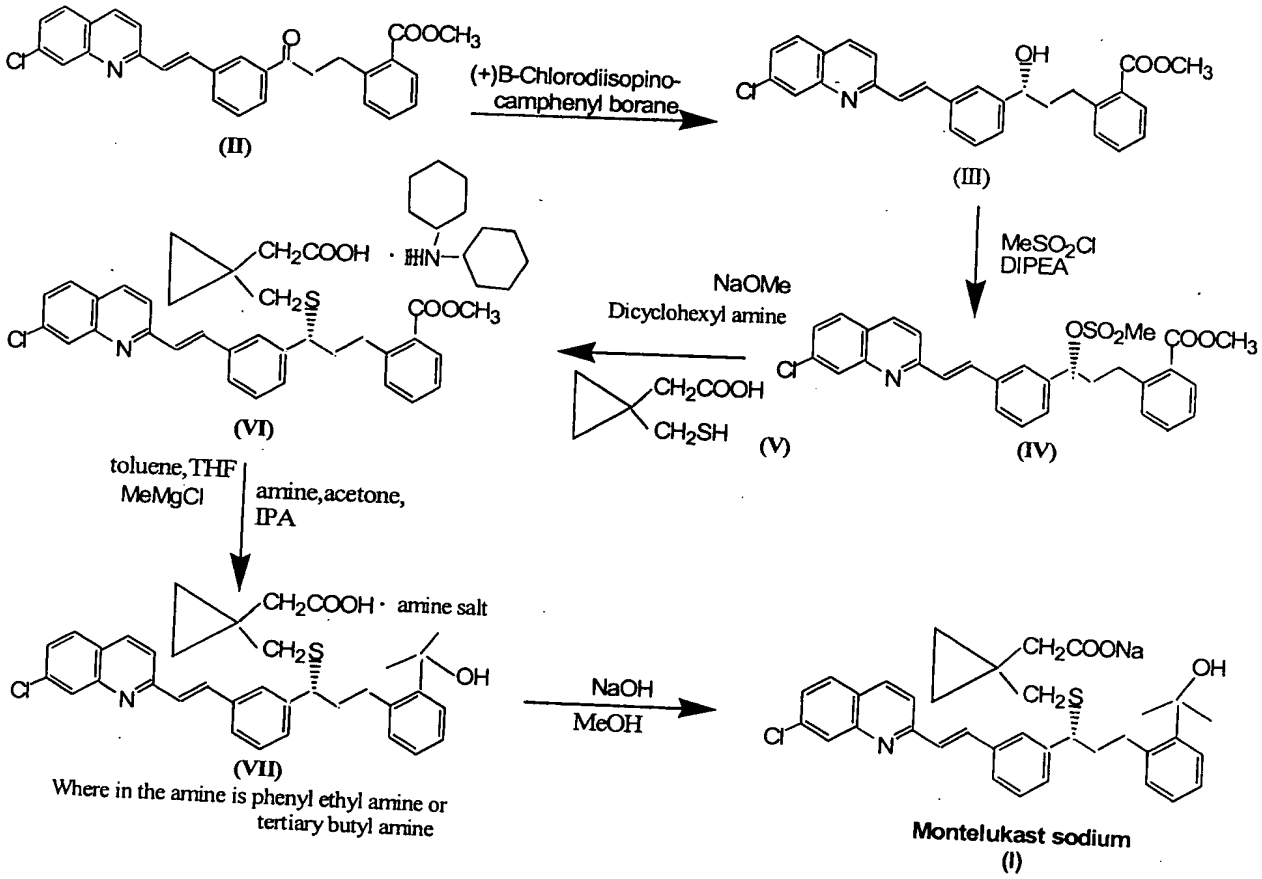
SUMMARY OF THE INVENTION:

The present invention provides an improved process for the preparation of Montelukast and its pharmaceutically acceptable salts, preferably sodium salt. The novel process of the present invention comprises, the reduction of Methyl-2-(3-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-oxopropyl benzoate using (+) B-chloro diisopinocampheylborane as a chiral reducing reagent and the resultant alcohol is mesylated followed by condensation with 1-mercapto methyl cyclopropane acetic acid to give an ester compound. The ester is reacted with methyl magnesium chloride to afford Montelukast, and it is isolated in the form of phenyl ethylamine or tertiary butyl amine salt. The amine salt of Montelukast is converted into sodium salt of Montelukast in a conventional method.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention relates to a novel and improved process for the preparation of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] Propyl] thio] methyl] cyclopropaneacetic acid (commonly known as Montelukast) and its pharmaceutically acceptable salts, preferably sodium salt.

The process of the present invention is schematically represented as follows.



Methyl-2-(3-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-oxopropyl benzoate of Formula (II) is reduced with (+) B-chloro diisopinocampheylborane as a chiral reducing reagent in polar organic solvents to result Methyl-2-(3-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-hydroxy propyl benzoate of Formula (III).

The compound of formula (III) is mesylated with methane sulfonyl chloride in a mixture of polar and non-polar organic solvents to form Methyl-2-(3-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-methane sulfonyloxy propyl benzoate of formula (IV), which is then condensed with 1-mercapto methyl cyclopropane acetic acid of formula (V) in mixture of polar organic solvents in presence of base and is isolated in the form of organic amine salt of formula (VI). The resultant amine salt is reacted with methyl magnesium chloride in an organic solvent to get Montelukast acid and is again converted to its organic amine salt of formula (VII) to get more pure compound. The amine salt of Montelukast of formula (VII) is conveniently converted into pharmaceutically acceptable salts, preferably sodium salt using sodium methoxide or sodium hydroxide.

Accordingly, the present invention provides an improved process for the preparation of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl]ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl]propyl]thio]methyl] cyclopropaneacetic acid (commonly known as Montelukast) and its pharmaceutically acceptable salts, preferably sodium salt, which comprises;

a) adding (+) B-chloro diisopinocampheylborane (a chiral reducing agent) to a haloalkane solvent comprising of dichloromethane, dichloroethane or chloroform, preferably dichloromethane or an ethereal solvent such as tetrahydrofuran under nitrogen atmosphere at a temperature of –25 to +20°C, preferably –5 to 10OC;

b) adding the solution of Methyl-2- (3-(3-(2-(7-chloro-2-quinolinyl) ethenyl) phenyl)-3-oxopropyl benzoate of Formula (II) in organic solvent described as in step (a), at a temperature of –25 to +20°C, preferably –5 to 10°C followed by stirring the mass till the reaction substantially completes;

c) further quenching the mass with either organic or inorganic base and subsequent work up to get an alcohol of formula (III);

d) reacting the alcohol obtained in step (c) with methane sulfonyl chloride in presence of tertiary amines comprising of diisopropyl ethyl amine or triethyl amine as base in a polar and non-polar or mixture of organic solvents at a temperature of 0-75°C;

e) stirring the reaction mass obtained in step (d) till the reaction substantially completes and subsequent work up to get mesylated compound of formula (IV);

f) reacting mesylated compound of formula (IV) with 1-mercapto methyl cyclopropane acetic acid of formula (V) in polar organic solvents or mixture of polar solvents in presence of base such as sodium methoxide, sodium ethoxide, sodium hydride or n-butyl lithium at a temperature of 30-90°C;

g) stirring the reaction mass obtained in step (f) till the reaction substantially completes and subsequent work up to get crude ester compound and further reaction with dicyclohexyl amine salt to afford the amine salt of formula (VI);

h) treating the amine salt of formula (VI) with an organic acid such as acetic acid and further reaction with methyl magnesium chloride or methyl magnesium bromide in an organic solvents such as tetrahydrofuran, diethyl ether, diisopropyl ether, 2-methoxy ethanol, toluene, ethyl benzene, 1,4-dioxan or mixture thereof at a temperature of −10 to +50°C;

i) stirring the reaction mass obtained in step (h) till the reaction substantially completes and subsequent work up to isolate the Montelukast acid from polar and nonpolar solvents such as toluene, ethyl acetate, acetonitrile, heptane and

hexanes; purifying the obtained acid compound selecting from polar solvents such as toluene ,methanol, ethanol, isopropanol, n-propanol, ethyl acetate, methyl acetate, acetonitrile or mixture thereof and the resultantant Montelukast free acid further reaction with primary, secondary or tertiary amines, preferably tertiary butyl amine or phenyl ethyl amine to afford the amine salt of formula (VII);

j) purifying the amine compound obtained in step (i) in an organic solvent selected from toluene ,methanol, ethanol, isopropanol, n-propanol, ethyl acetate, methyl acetate, acetonitrile or mixtures thereof;

k) converting the amine salt into its pharmaceutically acceptable salts by;generating the Montelukast free acid from Montelukast amine salt in haologinated solvents selected from chloroform ,dichloromethane or dichloroethane, particularly dichloromethane or aromatic hydrocarbons selected from toluene, ethyl benzene or xylene particularly toluene using an organic acid such as acetic acid;

l) distilling the solvent of step (k) under reduced pressure at below 60°C till the residual mass obtains;

m) dissolving the free acid of step (l) in halogenated solvents selected from chloroform, dichloromethane or dichloroethane, particularly dichloromethane or aromatic hydrocarbons selected from toluene, ethyl benzene or xylene, particularly toluene;

n) conversion of reaction solution of step (m) into sodium salt using sodium hydroxide, sodium methoxide or sodium ethoxide in alcohols selected from methanol, ethanol, propanol, butanol, 2-propanol or tert.butanol, preferably methanolic sodium hydroxide;

o) distillation of solvent from reaction solution of step (n) under reduced pressure and dissolving the residue in toloune, ethylbenzene, dichloromethane;

p) isolation of desired product from step (o) by adding cyclohexane,n-heptane & hexanes ;

q) drying the powder at 50-80°C under high vacuum.

The Montelukast sodium obtained in the present novel process is having >99.0% enantiomeric excess purity and resulted in amorphous form. The Montelukast sodium obtained in the present novel process is also free flowing and non-solvated solid; hence it is well suited for pharmaceutical applications.

The process of the present invention is cost effective, eco-friendly and well suited for scale up.

EXAMPLES

EXAMPLE-1

Methyl 2 - (3 - R - (3- (2- (7- chloro 2- quinolinyl) - ethenyl) - 3 hydroxy propyl) benzoate.

(+) – Diisopino campheylchloroborane (398 ml), dichloromethane (1000 ml) charged into RBF under nitrogen atmosphere, methyl -2- (3- (3- (2- (7-chloro-2-quinolinyl ethenyl) phenyl)-3- oxo propyl - benzoate (200 gms.) dissolved in dichloro methane (1000 ml) separately at 25-35°C; added this solution to the above reaction mass slowly at 0°C to 5°C under nitrogen atmosphere, maintained at 0 -5°C upto reaction completion, charged aqueous ammonia (25 % W/V) (130 ml) to the reaction mass under stirring, then cooling removed and stirred at 25°-35°C for 1-2 hours. Charged 20 % vacuum salt solution to the reaction mass under stirring and continued for 15-30 minutes.

Separated the organic and aqueous layer, organic layer washed with 3 x 200 ml of 20 % vacuum salt solution. Distilled off the solvent from organic layer at atmospheric pressure at below 55°C, and finally traces removed under reduced pressure. Obtained crude dissolved in methanol (400 ml) and again distilled methanol under reduced pressure at below 55°C. Thus the obtained crude dissolved in methanol (2400 ml) at 25-35°C, and stirred at 25-35°C for 1-2 hours. Filtered the undissolved gum material and gum washed with methanol (200 ml). Filtrate transferred into fresh RBF and added water (600 ml) slowly drop wise under stirring in 2-3 hours to precipitate the compound and stirring continued for further 1-2 hours. Filtered the solid and washed with a mixture of methanol (100 ml) and water (100 ml). Finally washed with hexanes (400 ml) and dried at 50-60°C to afford the 142 grams of title compound.

EXAMPLE – 2

Purification of methyl 2 - (3 - R - (3- (2- (7- chloro 2- quinolinyl) - ethenyl) - 3 hydroxy propyl) benzoate.

Methyl 2 - (3 - R - (3- (2- (7- chloro 2- quinolinyl) - ethenyl) - 3 hydroxy propyl) benzoate (142grams) dissolved in methanol (1704 ml) and stirred at 25-35°C for 1 hour. Filtered the undissolved gum material and gum washed with methanol (142 ml). Combined filtrate transferred into fresh RBF and added water (426 ml) slowly drop wise at 25-35°C in 2-3 hours to precipitate the compound and stirring continued for further 1-2 hours at 25-35°C. Filtered the solid compound and washed with a mixture of methanol (71 ml) and water (71 ml). Finally washed with hexanes (284 ml) and dried at 50-60°C to afford 103.1 grams of title compound.

EXAMPLE - 3

Dicyclohexyl amine salt of 2-[1-[1- R -3- [2- (7 chloro quinolin -2- yl) vinyl [phenyl] -3- [2 - methoxy carbonyl phenyl] propyl sulfonyl methyl] cyclo propyl] acetic acid

Methyl 2 – (3 R - (3 – (2 – (7 – Chloro 2- Quinolinyl) – ethenyl phenyl) –3- hydroxy prepyl) benzoate (100 grams) and toluene (500 ml) charged into RBF and stirring and given. Heating given and maintained at reflux temperature for 1 hour then distilled off toluene (~ 300 ml) at atmospheric pressure through azotrepically, reaction mass cooled to 50°C, and remaining solvent distilled under reduced pressure. Dissolved the residual product in dichloro methane (200 ml) at 25-35°C and distilled off the solvent completely under reduced pressure. Ressidue dissolved in dichloro methane (1000 ml) at 25-35°C under stirring and cooling given; charged diisopropyl ethylamine (305 ml) at once at 0-5°C. Reaction mass stirred at 0-5°C for 15-30 minutes. Added methane sulfonyl chloride (84.6 ml) slowly drop wise at 0-5°C under stirring. Cooling removed, reaction mass maintained at 25-35°C upto reaction completion. Gharged water (600 ml) and stirred for 30 minutes. Separated the organic and aqueous layer and aqueous layer extracted with dichloro methane (200 ml). Combined the organic layer and washed with water (3 x 600 ml). Distilled off dichlorochloro methane atmospherically followed by under reduced pressure at below 50°C, obtained residual product dissolved in toluene (200 ml) and again distilled

off completely under reduced pressure at 45-50°C till the residual mesylate product obtained.

Charged mercapto methyl cyclopropyl acetic acid (47.9 grams), methanol (450 ml) and stirred for clear dissolution at 25-35°C for 60 minutes. Mixture of above mesylate product, dichloromethane and dimethyl formamide (450 ml) solution added to reaction mass and stirred for clear dissolution at 25-35°C, heating given for reflux. Reaction mass maintained at reflux temperature for 2-3 hours. Charged water (450 ml) to reaction mass and stirred for 15 minutes, separated the organic and aqueous layer and aqueous layer extracted with dichloro methane (200 ml). Combined the organic layer and washed with a mixture of vacuum salt (37.5 grams) and water (400 ml) solution, then washed with acetic acid (45 ml) and water (400 ml) solution followed by water (4 x 400 ml).

Distilled off the solvent from the organic under atmospherically and finally traces removed under reduced pressure at 45-50°C. Dissolved the residual product in acetone (200 ml) and again acetone distilled off completely under reduced pressure at 45-50°C. Thus obtained residual crude product dissolved in acetone (500 ml) at 25-35°C, charged dicyclo hexyl amine (51.6 ml) at 25-35°C. and stirred at 25-35°C untill thick solid separation. Filtered the compound and wet cake charged into acetone (400 ml) and heating given for reflux. Maintained at reflux temperature for 1-2 hours and cooled to 25-35°C, stirring continued for 4-5 hours. Finally filtered the solid product and washed with acetone (50 ml). Wet compound dried in oven at 45-50°C to afford the 49.7 grams of the desired product.

EXAMPLE – 4

Purification of dicyclo hexyl amine salt of 2 - [1 - [1 - (R) -3- [2- (E) - (7chloro quinolin -2- yl) vinyl [phenyl] –3- [2 – methoxy carbonyl phenyl] propyl sulfonyl methyl] cyclo propyl] acetic acid.

Charged dicyclo hexyl amine salt of 2 - [1 - [1 - (R) -3- [2- (E) - (7chloro quinolin -2- yl) vinyl [phenyl] –3- [2 – methoxy carbonyl phenyl] propyl sulfonyl methyl] cyclo propyl] acetic acid (49 grams) and acetone (490 ml) into RBF and heating given for reflux. Maintained at reflux for 1-2 hours and cooled to 25-35°C slowly under stirring. Reaction mass maintained at 25-35°C for 4-5 hours. Filtered the separated solid compound and

washed with acetone (49 ml). Compound dried in oven at 50-55°C to afford 44.7 grams of purified title compound.

Example-5

[R]-1- [[[1- [3- [2- (7-chloro-2-quinolinyl) ethenyl] phenyl]-3-[2- (1-hydroxy-1-methyl ethyl)-phenyl] propyl] thio]methyl] cyclopropane acetic acid (Montelukast acid).

Charged dicyclohexyl amine salt of 2 -[1 - [1 - (R) -3- [2- (E) - (7chloro quinolin -2- yl) vinyl [phenyl] –3- [2 – methoxy carbonyl phenyl] propyl sulfonyl methyl] cyclopropyl] acetic acid (100 grams), toluene (1000 ml) in to RBF, stirred for 5 minutes. Charged a mixture of acetic acid (15 ml) and water (500ml), stirred for 30 minutes. Separated the organic layer and aqueous layer, organic layer washed with water (3x500 ml) and dried over Sodium Sulphate. Distilled off solvent completely under reduced pressure at below 50°C. The resulted crude dissolved in mixture of toluene (760 ml) and tetrahydrofuran (760 ml), transferred the reaction solution into RBF and cooled to 0°C under nitrogen atmosphere, added 3 molar methyl magnesium chloride (261 ml) in tetrahydrofuran drop wise in 2-3 hours at 0-5°C, reaction mass maintained at 0-5°C for 6-7 hours. Cooled the reaction mass to 0 °C and added slowly a mixture of acetic acid (90 ml) and water (750 ml) at below 15°C for about one hour. Reaction mass stirred at 25-35°C for one hour to get clear dissolution, separated organic and aqueous layer, organic layer washed with 5%sodium bicarbonate solution (2x750 ml) followed by water (2x750 ml). Organic layer dried over sodium sulphate and distilled off the solvent completely under reduced pressure till the residual product obtained. Taken the residual compound and repeated the above Grignard process followed by its work up two to three times till the completion of the Grignard reaction (check for absence of starting material).

Finally Crude dissolved in toluene (100 ml) and stirred at 25-35°C till thick solid separation. Filtered the solid and washed with toluene (30 ml). Wet compound and toluene (90 ml) charged into RBF and heated to 90 °C, stirred for 30 minutes for complete dissolution, cooled to 25-35°C and maintained for 6-10 hours. Solid filtered washed with toluene (22 ml). Repeated this recrystalization process for four to five times to get the

compound with good quality. Dried the obtained compound to afford 17.4 grams of the title product.

Example-6

[R]-1- [[[1- [3- [2- (7-chloro-2-quinolinyl) ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl)-phenyl]propyl] thio]methyl] cyclopropane acetic acid tertiary butyl amine salt (Montelukast tertiary butyl amine salt).

Charged [R]-1-[[[1-[3- [2-(7-chloro-2-quinolinyl) ethenyl] phenyl]-3- [2- (1-hydroxy-1-methyl ethyl)-phenyl] propyl] thio] methyl] cyclopropane acetic acid (8.6 grams), acetone (155 ml) and isopropyl alcohol (17 ml) into RBF and stirred at 25-35°C up to clear dissolution. Added tertiary butyl amine and stirred at 25-35°C up to thick solid separation. Filtered the product and washed with acetone (20 ml) and dried at 40-50°C. Recrystallization of the above product in a mixture of acetone (225 ml) and isopropyl alcohol (25 ml), affords 6 grams of the title product.

Example-7

[R]-1- [[[1- [3- [2- (7-chloro-2-quinolinyl) ethenyl] phenyl]-3- [2- (1-hydroxy-1-methyl ethyl)-phenyl] propyl] thio]methyl] cyclopropane acetic acid sodium salt (Montelukast sodium salt).

Charged [R]-1- [[[1- [3- [2- (7-chloro-2-quinolinyl) ethenyl] phenyl]-3- [2- (1-hydroxy-1-methyl ethyl)-phenyl] propyl] thio] methyl] cyclopropane acetic acid tertiary butyl amine salt (Montelukast tertiary butyl amine salt) and dichloromethane (50 ml) into RBF at 25-35°C. Added acetic acid (0.5ml) and water (25 ml) mixture to the reaction mass, stirred at 25-35°C for 15 minutes. Separated the organic layer and aqueous layer. Washed the organic layer with water (4x25 ml) and dried over sodium sulphate. Distilled off solvent completely under reduced pressure at below 45°C. Added methanol (10 ml) to residual mass and distill off solvent completely under reduced pressure at below 45°C. Freshly prepared Sodium (0.307 grams) pellets and methanol (50 ml) mixture added to the residual

mass at 25-35°C. Added carbon (0.5 grams) and stirred for 30 minutes at 25-35 °C. Filtered the carbon and washed with methanol. Distilled off solvent completely under reduced pressure at below 45°C. Obtained crude dissolved in toluene (25 mi) and distilled off solvent completely under reduced pressure at below 45°C. Finally crude dissolved in toluene (5 ml) and added to the pre filtered n-heptane under nitrogen atmosphere at 25-35°C. Maintained the reaction mass at 25-35°C forl hour. Filtered the compound and washed with n-heptane (25 ml) under nitrogen atmosphere. Dried the compound at 80°C for 4-5°C to afford 3.2 grams of the title product.

We claim:

1.A process for the preparation of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast Sodium), from Montelukast amine salt or Montelukast free acid which comprises:

(i) generating the Montelukast free acid from Montelukast amine salt in halogenated solvents selected from chloroform, dichloromethane or dichloroethane,particularly dichloromethane or aromatic hydrocarbons selected from toluene, ethyl benzene or xylene, particularly toluene using an organic acid such as acetic acid;

(ii) dissolving the Montelukast free acid or free acid of step (i) in halogenated solvents selected from chloroform, dichloromethane or dichloroethane, particularly dichloromethane or aromatic hydrocarbons selected from toluene, ethyl benzene or xylene, particularly toluene;

(iii) conversion of reaction solution of step (i) or step (ii) into sodium salt using sodium hydroxide, sodium methoxide or sodium ethoxide in alcohols selected from methanol, ethanol, propanol, butanol, 2-propanol or tert.butanol, preferably methanolic sodium hydroxide;

(iv) isolation of desired product by adding a cyclic or acyclic hydrocarbons by conventional methods and

2. A process according to claim 1 of step (i) wherein Montelukast amine salt is Montelukast tertiary butyl amine or Montelukast phenyl ethylamine salt.
3. A process according to claim 1 of step (iii) wherein the alcoholic base solution is methanolic sodium hydroxide.
4. A process according to claim 1 of step (iv) wherein the cyclic hydrocarbon solvent is cyclohexane and acyclic hydrocarbon is hexane or n-heptane.
5. A process for the preparation of Montelukast tertiary butyl amine salt, Montelukast phenyl ethyl amine salt from Montelukast free acid in polar solvents such as acetone, methyl ethylketone, methyl isobutylketone, methanol, ethanol, isopropanpol, n-propaanol, n-butanol, ethyl acetate, acetontrile or mixture thereof.

6. A process for the purification of Montelukast tertiary butyl amine or Montelukast phenyl ethyl amine salt and Montelukast free acid in polar solvents such as acetone, methyl ethylketone, methyl isobutylketone, methanol, ethanol, isopropanpol, n-propaanol, n-butanol, ethyl acetate, acetontrile or mixture thereof.
7. A process for the preparation of Montelukast acid on reaction of Dicyclohexyl amine salt of 2-[1-[1- R -3- [2- (7 chloro quinolin -2- yl) vinyl [phenyl] -3- [2 - methoxy carbonylphenyl] propyl sulfonyl methyl] cyclo propyl] acetic acid compound with methyl magnesium bromide or methyl magnesium chloride in polar solvents such as toluene, tetrahydrofuran, diethyl ether, and diisoprpyl ether.
8. A process for the preparation of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast Sodium), from Montelukast amine salt or Montelukast free acid as herein described and exemplified.

Dated 24th day of December 2003

Signed S. Venkatraman
Sunderam Venkatraman
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Abstract:

The present invention provides an improved process for the preparation of Montelukast and its pharmaceutically acceptable salts, preferably sodium salt. The novel process of the present invention comprises, the reduction of Methyl-2-(3-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-oxopropyl benzoate using (+) B-chloro diisopinocampheylborane as a chiral reducing reagent and the resultant alcohol is mesylated followed by condensation with 1-mercapto methyl cyclopropane acetic acid to give an ester compound. The ester is reacted with methyl magnesium chloride to afford Montelukast, and it is isolated in the form of phenyl ethylamine or tertiary butyl amine salt. The amine salt of Montelukast is converted into sodium salt of Montelukast in a conventional method.